

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/78, C12N 15/62, 5/10, A61K 48/00	A1	(11) International Publication Number: WO 98/38303 (43) International Publication Date: 3 September 1998 (03.09.98)
(21) International Application Number: PCT/GB98/00468 (22) International Filing Date: 2 March 1998 (02.03.98) (30) Priority Data: 9704305.3 <i>01 Sep 99/30 nos</i> 1 March 1997 (01.03.97) GB (71) Applicant (for all designated States except US): THE VICTORIA UNIVERSITY OF MANCHESTER [GB/GB]; Oxford Road, Manchester M13 9PL (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): BULLEID, Neil, John [GB/GB], 25 Gaddum Road, Didsbury, Manchester M20 6SY (GB). (74) Agent: ATKINSON, Peter, Birch; Marks & Clerk, Sussex House, 83-85 Mosley Street, Manchester M2 3LG (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PROCOLLAGEN ASSEMBLY (57) Abstract A method of producing a desired procollagen or derivative thereof in a system which co-expresses and assembles at least one further procollagen or derivative thereof. The gene(s) for expressing pro- α chains or derivatives thereof for assembly into the desired procollagen has or have been exogenously selected from natural pro- α chains or exogenously manipulated such as to express said pro- α chains or derivatives thereof with domains which have the activity of C-terminal propeptide domains but which will not co-assemble with the C-terminal propeptide of the pro- α chains or derivatives thereof that assemble to form the said at least one further procollagen or derivative thereof.		

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PBA/D087882PWO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 98/00468	International filing date (day month year) 02/03/1998	(Earliest) Priority Date (day month year) 01/03/1997
Applicant THE VICTORIA UNIVERSITY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **4** sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).
2. ☐ **Unity of invention is lacking** (see Box II).
3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☒ furnished by the applicant separately from the international application.
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the **title**, ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
 - ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority
6. The figure of the **drawings** to be published with the abstract is

Figure No.

☐ as suggested by the applicant
☐ because the applicant failed to suggest a figure.
☐ because this figure better characterizes the invention

☒ None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/00468

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 26 and 27
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 98/00468

A CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/78 C12N15/62 C12N5/10 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched: classification system followed by classification symbols

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category: Citation of document with indication, where appropriate, of the relevant passages

Relevant to claim No.

X	<p>WO 93 07889 A (UNIV JEFFERSON) 29 April 1993 cited in the application see abstract; figures 1.4; examples 1.2.6; table 1</p>	<p>1-6, 12, 17-21</p>
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A	<p>LEES J F AND BULLEID N J: "The role of cysteine residues in the folding and association of the COOH-terminal propeptide of types I and III procollagen" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 39, 30 September 1994, pages 24354-24360, XP002071356 cited in the application see abstract; figures 1,10 see section results</p>	
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☒ Further documents are listed in the continuation of this page

☒ Patent family members are listed in annex

Relevant categories of cited document:

- A document defining the general state of the art which is not considered to be of particular relevance
- E earlier document but published on or after the international filing date
- L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason has specified
- O document referring to an oral disclosure, use, exhibition or other means
- P document published prior to the international filing date but after the priority date claimed

71 later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- Z document member of the same patent family

Date of the actual completion of the international search

Date of making of the international search report

15 July 1998

28.07.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentamt 2
JUL 2280 H V Rijswijk
Tel. (+31-70) 340-2040, Tx. (+31-65) 86000
Fax (+31-70) 340-3016

Authorized officer

Oderwald, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00468

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 699 752 A (COLLAGEN CORP) 6 March 1996 see the claims see abstract: examples 2,3 ---	
X,P	WO 97 08311 A (UNIV MANCHESTER; BULLEID NEIL (GB); KADLER KARL (GB)) 6 March 1997 cited in the application see abstract: figures 1,3,4 see page 2 - page 3 see page 5, paragraph 3 - page 13, paragraph 2 see page 16 - page 22 ---	1-27
X,P	LEES J F ET AL: "Identification of the molecular recognition sequence which determines the type-specific assembly of procollagen" EMBO JOURNAL, vol. 16, no. 5, 3 March 1997, pages 908-916, XP002071357 see the whole document ---	1-4,6, 11-22
X,P	MYLLYHARJU J ET AL: "Expression of wild-type and modified proalpha chains of human type I collagen in insect cells leads to the formation of ..." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 35, 29 August 1997, pages 21824-21830, XP002071358 see the whole document -----	1-3,6, 11-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/00468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9307889 A	29-04-1993	AU 680606 B	07-08-1997
		AU 3055592 A	21-05-1993
		AU 4441497 A	12-02-1998
		CA 2121698 A	29-04-1993
		EP 0625048 A	23-11-1994
		JP 7501939 T	02-03-1995
		US 5405757 A	11-04-1995
		US 5593859 A	14-01-1997
EP 0699752 A	06-03-1996	NONE	
WO 9708311 A	06-03-1997	AU 6832696 A	19-03-1997

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/00468

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos. because they relate to subject matter not required to be searched by this Authority, namely:
 Remark: Although claim(s) 26 and 27 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos. because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a):

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ATTENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

United States Patent and Trademark
Office
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Crystal Plaza 2
Washington, DC 20231
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(not applicable to elected Office)

Date of mailing

03 September 1998 (03.09.98)

International application No.

PCT GB98 00468

Applicant's agent of reference

PBA D037882PWO

International filing date

02 March 1998 (02.03.98)

Priority date

01 March 1997 (01.03.97)

Applicant

BULLEID, Neil, John

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on

06 August 1998 (06.08.98)



in a notice effecting election filed with the International Bureau on

2. The election ☒ was



made at

in compliance with the provisions of the International Patent Cooperation Treaty, Article 26, paragraph 2, and the Regulations under the Treaty, Rule 12.2.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

PATENT COOPERATION TREATY

PCT

REC'D 16 JUN 1999

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

APR 24 2000

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Applicant's or agent's file reference ---	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB98/00468	International filing date (day/month/year) 02/03/1998	Priority date (day/month/year) 01/03/1997
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant THE VICTORIA UNIVERSITY OF MANCHESTER et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 06/08/1998	Date of completion of this report 7. 00. 33
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Heckl, K Telephone No. (+49-89) 2399 8430 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

APR 24 2000

International application No. PCT/GB98/00468

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-30 as originally filed

Claims, No.:

1-27 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1-10, 12, 16 all compl., 13-15, 17-27 all part..

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/00468

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-10,12,16 all compl., 13-15,17-27 all part. are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11,13-15,17-21 part.
	No:	Claims	11,13-15,17-27 part.
Inventive step (IS)	Yes:	Claims	11,13-15,17-21 part.
	No:	Claims	11,13-15,17-27 part.
Industrial applicability (IA)	Yes:	Claims	11,13-15,17-21 part.
	No:	Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/00468

ad section I

1. With the letter dated 04.05.1999, Applicant submitted new claims 1-24. However, no basis could be found for the features newly introduced into claim 1. Therefore, these amendments cannot be allowable under Art.34(2)(b) PCT.
2. Therefore, this IPER has been based on claims 1-27 originally filed.

ad section III

1. Claim 1 does not indicate the solution of the problem which has been formulated as "to express said pro-alpha chains ... with domains which have the activity of the C-terminal propeptide domains but which will not co-assemble with ...". Therefore, claim 1 attempts to define the subject-matter in terms of the result to be achieved.

Also claim 2, requiring the presence of a recognition sequence does not help to overcome the above problem. In fact, there is neither indication of the nature of the recognition sequence, nor of its location.

The latter problem still adheres with claims 3-10.

2. The essential features of the present invention seem to be depicted in claim 11 as far as referring to claims 3-10. Claim 11 teaches that the gene encoding a pro-alpha chain comprises a recognition sequence derived from one pro-alpha chain and an alpha chain domain derived from a different source, in other words, claim 11 teaches the exchange of the recognition sequence. The nature of the recognition sequence is incorporated by referring to claims 3-10.

It follows that claim 11, as far as referring to claim 2 also suffers from the absence of the identification of the recognition sequence.

3. Claim 12 also involves problems upon interpretation. In fact, a "chimeric pro-alpha gene formed of at least two different pro-alpha chains" does not necessarily encompass the teaching of claim 11.

The same applies to claim 16.

4. Therefore, claims 13-15 can only be interpreted in a meaningful way by considering their dependencies on claim 11, exclusively.
5. The same applies, mutatis mutandis, to the subject-matter of claims 17-27.
6. Taken together, claims 1-10, 12, and 16, all complete, cannot be interpreted in a meaningful and therefore, cannot be subjected to IPE. The same applies to claims 13-15 and 17-27, all partially.

Therefore, claim 11 as far as referring to claims 3-10 and claims 13-15 and 17-27 as far as referring thereto, form the basis of this communication.

ad section V

1. The following documents are considered relevant prior art:

D1: WO93/07889

D2: JBC 269/39, 1994, 24354-60

2. Novelty (Art.33(2) PCT):

- 2.1 D1 discloses procollagen and collagen expression systems. Pro-alpha 1(I), 2(I), 1(II) and 1(III) are combined thus creating hybrid constructs (see examples 1, 2 and 6, claims 1-9 and 18-25). The expression product may have therapeutical use such as in the repair of cartilage damage (see page 10, line 20 to page 11, line 17).

Accordingly, the subject-matter of claim 11 as far as referring to claims 3-6 is not novel. In fact, the particular recognition sequences of claims 3-6 are comprised in the hybrid genes as disclosed in D1.

- 2.2 The same applies to claims 13-15 and 17-21 as far as referring thereto.

3. Inventiveness (Art.33(3) PCT):

- 3.1 The teaching that the gene encoding a pro-alpha chain comprises a recognition sequence derived from one pro-alpha chain and an alpha chain domain derived from a different source cannot be derived from the cited prior art in an obvious way.

In fact, D1 - though it discloses "methods for the production of (pro)collagens derived solely from transfected (pro)collagen genes" (see D1, page 10, lines 15-17) - it does neither teach nor suggest that the C-terminal part is responsible for strain-recognition and that this part is interchangeable within the different pro-alpha chain types.

Also D2 - though hypothesizing on the importance of the C-terminal part in chain discrimination during procollagen assembly (see D2, page 24360, last paragraph) - does not lead the skilled person to the teaching of claim 11.

Accordingly, the subject-matter of claim 11 as far as referring to claims 7-10 comprises an inventive step.

- 3.2 The same applies to claims 13-15 and 17-21 as far as referring thereto.

- 3.3 Selecting other hosts than those discloses in D1, including establishing and selecting a transgenic animal or plant as the host, cannot be considered as to comprise an inventive step.

Therefore, the subject-matter of claims 22-27 can only be considered inventive as far as depending on the inventive claims.

4. For the assessment of the present claims 26 and 27 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/00468

compound for the manufacture of a medicament for a new medical treatment.

5. The priority document of the present application has not been available at the time of establishing this IPER. Therefore, this IPER has been based on the assumption that the relevant parts of the claims enjoy the priority claimed.

Should it later turn out that this is not the case the P/X-documents cited in the International search report could become relevant to the subject-matter of the claims.